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Is Radiotherapy Useful for Treating Pain in Mesothelioma?
A Phase II Trial

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Introduction: Radiotherapy is often used to treat pain in malignant pleural mesothelioma (MPM), although there is limited evidence to support this. The aim of this trial was to assess the role of radiotherapy for the treatment of pain in MPM.

Methods: A multicentre, single arm phase II trial was conducted. Eligible patients fulfilled the following criteria: pathological or radiological diagnosis of MPM; pain secondary to MPM; radiotherapy indicated for pain control; and more than 18 years of age. Patients had assessments of pain and other symptoms at baseline and then received 20 Gy in five daily fractions. Key follow-up points were 5 and 12 weeks posttreatment. The primary end point measure was assessment of pain at the site of radiotherapy at 5 weeks. Secondary end points included effects on quality of life, breathlessness, fatigue, mood, toxicity, and the radiological response.

Results: Forty patients were recruited from three UK oncology centers. Fourteen patients had a clinically meaningful improvement in their pain 5 weeks post radiotherapy (intention to treat), with five patients having a complete improvement. On the basis of a complete case analysis of the 30 patients assessable at week 5, 47% (confidence intervals, 28.3–65.7) of patients alive at week 5 had an improvement in their pain. There was no improvement in other key symptoms or quality of life.

Conclusions: Radiotherapy for pain control in MPM is an effective treatment in a proportion of patients. Future studies examining differing radiotherapy regimens with a view to improving response rates are warranted.

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Malignant pleural mesothelioma (MPM) is a malignancy affecting the pleural lining. Exposure to asbestos is the most common etiological factor, and although it is a relatively rare malignancy, the incidence of MPM in the United Kingdom is among the highest in the world and is set to rise further in the next few years.[1,2] Its rarity is in contrast to its clinical effect. The median survival is 12 months, and lack of effective treatments means that it represents one of the main therapeutic challenges in Oncology.[3–5] As a result, the vast majority of patients are symptomatic of the disease and die from the condition.

MPM carries a high symptom burden, and pain is the most common. Various analgesics, including strong opioids, nonsteroidal anti-inflammatory drugs, anticonvulsants, local anesthetic agents, and steroids, are used. Despite these, pain control is often suboptimal.[6]

Over the last three decades, radiotherapy has been used as a key analgesic modality in MPM. Although this is widely accepted as a therapeutic option, a recent systematic review reported that there is limited evidence to support the role of radiotherapy in treating pain in MPM.[7] Studies to date have used a wide variety of doses and fractionation regimens, which have resulted in no clear consensus on the optimal radiotherapy regimen. Moreover, there have been no prospective studies using validated end points, although a previous study from Glasgow suggested some short-term benefit.[8] As a result, little can be drawn from these data in terms of informing practice. On the basis of the current evidence, which is mainly retrospective, the response rates using radiotherapy to treat pain in MPM vary from 0% to 69%. There is a need for prospective studies using standard radiotherapy regimens and validated end points, which examine radiotherapy for treating pain in MPM. Therefore, the SYSTEMS study was conducted to assess the role of radiotherapy for pain control in MPM using standard radiotherapy regimens, controlled background analgesia, and validated assessment tools.

MATERIALS AND METHODS

A multicenter, single arm, phase II study was conducted. The study had independent ethics committee approval (UK–12/

WS/0134) and was conducted in accordance with the Declaration of Helsinki. It was registered at the ISRCTN database (66947249). There was one major protocol modification, which was an amendment to include positron emission tomography–computed tomography (PET-CT) scanning to assess a possible role in radiotherapy planning in MPM. These findings will be presented elsewhere. This was discussed and approved by the Trial Steering Committee and occurred after 19 patients had been consented.

Patients

Eligible patients fulfilled the following criteria: 18 years of age or over; histological or agreed clinical and radiological diagnosis of MPM by thoracic oncology multidisciplinary team; due to receive radiotherapy (indication pain resulting from MPM); Eastern Cooperative Oncology Group performance status 0–2; CT scan within the previous 8 weeks; and had pain ≥4 of 10 (worst pain in the previous 24 hours) on a 0–10 visual analogue scale.

Patients who had received radiotherapy or chemotherapy in the preceding 6 weeks that was likely to alter pain during the duration of the trial or planned chemotherapy during the trial period were excluded.

The trial was conducted in three regional cancer centers in the United Kingdom (Beatson West of Scotland Cancer Centre, Edinburgh Cancer Centre, and Weston Park Hospital NHS Trust, Sheffield).

Trial Design

Before consent, all patients were assessed and had their current analgesia optimized. The aim of this was to stabilize analgesia before radiotherapy, with the purpose of minimizing the likelihood of changes in analgesia during the trial. This was undertaken to enable, where possible, the true effect of radiotherapy to be seen. Consenting patients would have stable but poorly controlled pain, necessitating the need for radiotherapy.

After obtaining written informed consent, all baseline assessments were performed. Patients then underwent radiotherapy planning and subsequently started treatment a maximum of 7 days from trial baseline.

Radiotherapy

Wire markings were placed on the skin to outline the outer limits of the painful area. Radiotherapy was planned using CT simulation either by CT field placement or by voluming of the tumor using an Eclipse workstation. All planning CTs were captured on LightSpeed Simulator LS RT 16 GE Medical CT scanner (GE Medical systems, Crawley, United Kingdom) using a 120 kV automatic mA modulation range of 15–240 mAs with 50 cm Dual Field of View. When the target area was contoured, the gross tumor volume was defined as the volume of tumor, which was felt to be responsible for the pain. This was then grown to a planning target volume (PTV) by 1–2 cm, subject to the discretion of the treating clinician. All patients were planned to receive 20 Gy in five fractions to the area of pain.

During the trial, assessments were performed at weeks 1, 5, and 12 after the start of radiotherapy. Patients were also contacted by telephone every week to monitor for any adverse events and assess analgesia.

End Points

The primary end point was level of pain 5 weeks after radiotherapy. An improvement in pain was defined as a ≥30% reduction in pain from baseline. Pain was assessed using the brief pain inventory (BPI), which has been extensively validated in cancer pain. An improvement of ≥30% is accepted as a clinically meaningful improvement in pain in studies of analgesic interventions.[9] Opioid analgesic use was recorded and is reported in morphine equivalent daily dose (MEDD) to allow comparison between different opioid types and to enable the effect of changes in analgesia with respect to changes in pain after radiotherapy.

Secondary end points assessed the effect of radiotherapy at weeks 1, 5, and 12 on the following: pain response at weeks 1 and 12; dyspnea assessed using a numerical rating scale; mood assessed using the Hospital Anxiety and Depression Scale; quality of life (QoL) using the EORTC QLQ-30; fatigue using the Fatigue Severity Scale (FSS); night sweats assessed using an numerical rating scale; radiotherapy toxicity as per common toxicity criteria for adverse events version 4.0; and the effect of radiotherapy on tumor bulk assessed by comparing CT scans at week 12 with baseline CT using the modified response evaluation criteria in solid tumors.[10]

Statistical Considerations

The statistical analysis was based on the objective of showing the proportion of patients for whom radiotherapy was an effective means of treating pain in MPM at 5 weeks post radiotherapy. A sample size of 40 patients was calculated to enable the proportion of responders to be estimated within ≤15%, depending on the true underlying proportion. An intention to treat (ITT) approach was used. The secondary end points were exploratory in nature.

All statistical analyses were performed using SPSS version 21.0 (Chicago, IL). Unless otherwise stated, means and standard deviations (SD) are used, and 95% confidence intervals (CI) are reported throughout. Patients who met the primary end point are termed "responders" and patients who did not are termed "nonresponders."

RESULTS

Patient disposition is shown in the CONSORT diagram in Figure 1. From June 2012 to December 2013, 40 patients consented to the trial. Of these, 37 patients started radiotherapy, with 35 completing their prescribed course. All sites of pain were in the chest.

Patient demographics are shown in Table 1. Thirty-five patients were male, and the median age (interquartile range [IQR]) was 71.50 (65.00–76.00) years. The most common histological type was epithelioid in 21 patients (56.8%), and the majority of patients were performance status 1 or 2. The median survival from the time of trial registration was 93 days (CI, 68–118). However, this differed depending on histological subtypes—epithelioid 124 days (83–165) versus sarcomatoid 65 (37–93), $p = 0.04$. The mean (SD) time from initial diagnosis to study entry was 249.41 days (274.16). The median (IQR) baseline BPI score was 57 (42.0–65.5), and the median (IQR) baseline opioid dose was 55 mg (25–210).

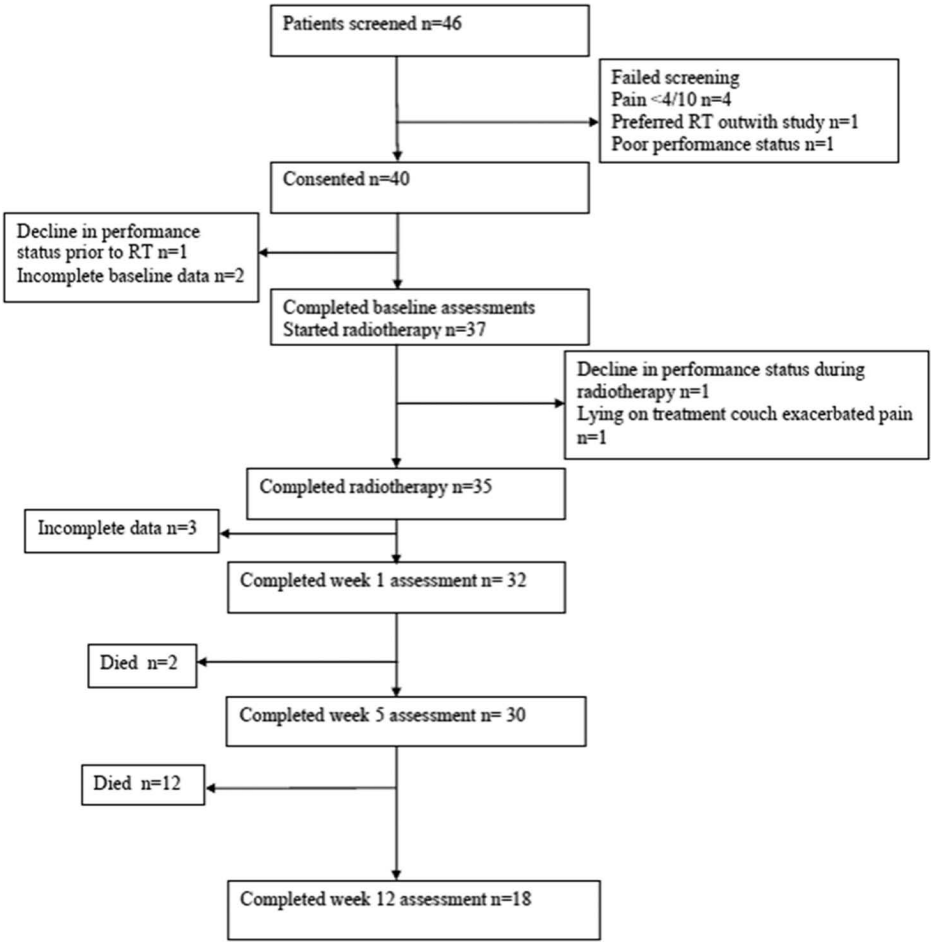

FIGURE 1. Patient disposition.

At the time of primary end point assessment (week 5), 30 patients were evaluable. Three patients did not start radiotherapy, two patients failed to complete radiotherapy, two patients had died before week 5, and three further patients had deteriorated to the point that they were no longer able to complete the assessment (Fig. 1). The primary end point, based on an ITT analysis, was met by 14 patients (35%) who had a clinically significant improvement in pain 5 weeks post radiotherapy. Nine patients (22.5%) had an improvement of ≥60% in BPI score with five patients (12.5%) having a complete response (100% improvement in BPI). Therefore, based on a complete case analysis of 30 evaluable patients at week 5, 47% (CI, 28.3–65.7) of patients responded to the radiotherapy. Of the 14 patients who responded to radiotherapy, eight had epithelioid histology, four had sarcomatoid, and two had mixed histology. As a percentage of the total number of each of these histological subtypes, 38% of epithelioid patients responded, 40% of sarcomatoid, and 66.6% of mixed histology. There was no statistically significant difference between histological subtypes in terms of response.

At weeks 1 and 12, the pain response rate was 27.5% (CI, 14–6% to 43.9%) and 15.0% (CI, 5.7–29.8%), respectively, on an ITT analysis. On the basis of a complete case analysis, the proportion of pain responders at week 1 was 36.7% (CI, 19.9–56.1%) and at week 12 was 33.3% (CI, 13.3–59.0%). Although 32 patients completed the week 1 assessment, two of them had incomplete data and so were not evaluable. Eighteen patients were evaluable at week 12.

Figure 2 shows changes in opioid dose and pain (BPI) per responder status. Only four responders had an increase in their opioid dose between study baseline and end point, and in only one patient was this >20 mg (MEDD). There was no difference in mean opioid dose between baseline and end point in the responders, $p = 0.627$. There was no difference in the percentage change from baseline MEDD at week 1 ($p = 0.577$) or week 5 ($p = 0.355$) between responders and nonresponders. Of the 14 responders, nine were on simple and eight on adjuvant analgesics at baseline. A similar proportion (16 of 24) of the nonresponders was on simple analgesics at baseline. Although a slightly higher proportion (17 of 24) of nonresponders was on adjuvant analgesics at baseline compared with responders, this was not statistically significant, $p = 0.391$. Throughout the duration of the study, only one patient was started on an adjuvant analgesic. Therefore, the improvement in pain is likely due to radiotherapy rather than analgesia.

There was no change in global QoL for patients throughout the study when they are taken as a whole group. However, there was a trend suggesting an improvement in QoL in responders and a decline in global QoL in nonresponders, although this was not statistically significant. The

TABLE 1. Patient Demographics

Characteristic	n	%	Mean	SD	Median	IQR
Age					71.50	65.00–76.00
Male	35	87.5				
ECOG						
0	3	7.5				
1	18	45.0				
2	19	47.5				
Time from diagnosis to trial entry (days)			249.41	274.16		
Mesothelioma						
Histology						
Epithelioid	21	56.8				
Sarcomatoid	10	27				
Mixed	3	8.1				
Other	3	8.1				
Not available	3	8.1				
Metastases						
Present	12	30.0				
Absent	27	71.1				
Unknown	1	2.5				
Previous anticancer therapy for MPM						
Chemotherapy	14	36.8				
Radiotherapy	1	2.5				

SD, standard deviation; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group.

median improvement in QoL in responders was 12.50 (IQR, −16.67 to 41.67) compared with a median decline of 12.50 (IQR, −25.00 to 0.00) in nonresponders. In terms of specific QoL components, there was a worsening of fatigue, appetite loss, and nausea/vomiting scores. Fatigue scores at week 12 ($p = 0.040$) and nausea/vomiting at week 1 ($p = 0.017$) had significantly increased. There were, however, improvements in pain, dyspnea, insomnia, and constipation. Pain scores at weeks 1 ($p = 0.005$) and 5 ($p = 0.034$) and dyspnea at week 1 ($p = 0.037$) were significantly lower. There was no significant difference between responders and nonresponders in the change in dyspnea score at week 5 (responders: median change, 0; IQR, −33 to 33; nonresponders: −16.67, IQR −33 to 0; $p = 0.203$). The greater improvement in nonresponders may be due to baseline dyspnea score being higher than for responders, although not significantly so ($p = 0.148$). Only one patient had a cough, which was recorded as grade 2 at all times including baseline.

The effect of radiotherapy on other key symptoms is shown in Table 2. There was no significant change in any other secondary end points with the exception of night sweats, which improved by week 5 ($p = 0.01$).

In Table 3, the percentage of patients with the most common symptoms and likely side effects from radiotherapy are reported. Only one patient had a delay in delivery of their radiotherapy because of radiotherapy induced odynophagia, however, this patient had an apical tumor, and their larynx was within the radiotherapy field. The patient had been given additional analgesia as prophylactic cover but had not taken it. On commencing the analgesia, the patient's odynophagia improved considerably, and he completed the radiotherapy.

Changes in disease bulk, assessed using CT, are shown in Table 4. Only 18 patients were alive and well enough to undergo the week 12 CT. Of these, there was only one partial response as assessed by the modified response evaluation criteria in solid tumors criteria for assessment of response in MPM.[10] None of the five patients who had radiological progressive disease had a drop in their BPI score.

The median PTV was 1046.70 cm^3 (IQR, 731.50–1339.90). There was no difference between the median PTV for responders—1004.00 cm^3 (IQR 585.20–1312.00)—and non responders—1104.85 cm^3 (IQR, 795.00–1356.85) suggesting that the size of the PTV does not correlate with the magnitude of response.

Median survival of responders was 106 days (95% CI, 86–126 days). Median survival was slightly lower in nonresponders at 93 days (95% CI, 18–168 days), but the difference was not statistically significant ($p = 0.465$).

DISCUSSION

This is the largest trial to date that examines the role of radiotherapy in MPM and the first to use validated assessment tools in this setting. The findings support that radiotherapy is an effective treatment for a proportion of patients with MPM-related pain with 35% of assessable patients experiencing a clinically meaningful improvement in their pain. Of these, 12.5% had a complete improvement in their pain. There was no association between pain response and

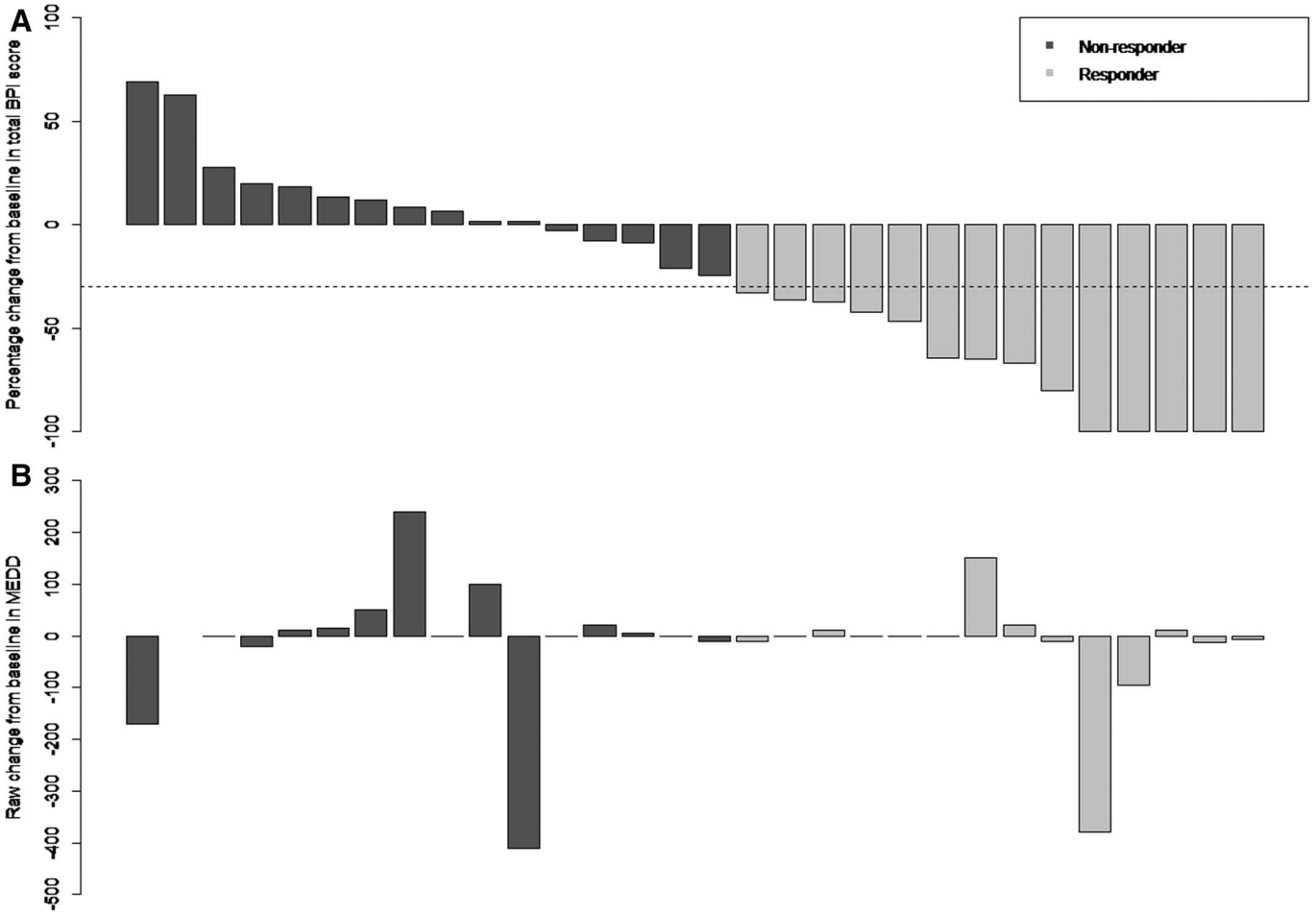

FIGURE 2. *A,* Waterfall plot of percentage change from baseline to week 5 in total BPI score and (*B*) corresponding raw change from baseline to week 5 in morphine equivalent daily dose. The dotted line indicates a 30% reduction from baseline BPI score, the "response" criterion. Note, a further 10 patients were classed as nonresponders, but have missing baseline and/or week 5 BPI total score.

improvement in any other symptoms, and therefore, palliative radiotherapy in MPM should only be considered for pain control.

There has been a lack of previous work in this area, with which to compare our findings. The only other prospective study that has examined radiotherapy in MPM reported 22 patients who were treated with hemithoracic irradiation using Cobalt-60 machines at a dose of 30 Gy in 10 fractions. Pain scores improved in 13 patients 1 month after radiotherapy with no increase in analgesic requirements. Validated pain assessment tools were not used in this study, though none were available at the time.[8]

The findings of the present study are, therefore, of interest and provide evidence to support radiotherapy as a useful modality for treating pain in MPM. Of particular note was that in 12.5% of patients a complete analgesic response was noted. This provides grounds for optimism for future work in this area. Future work should examine dose escalation, both in terms of total dose and dose per fraction, because the likelihood of improving outcomes by increasing dose

TABLE 2. Symptom Assessments Between Trial Baseline and Other Timepoints

Symptom (score)	Baseline mean (SD)	Week 1 mean (SD)	*P* Value	Week 5 mean (SD)	*P* Value	Week 12 mean (SD)	*P* Value
Dyspnea (0–10)	4.46 (2.47)	4.19 (2.84)	0.44	5.26 (2.35)	0.09	4.95 (3.08)	0.263
Sweats (0–10)	3.44 (3.58)	3.16 (3.29)	0.22	2.00 (3.02)	0.01	1.79 (2.74)	0.425
HADS anxiety (0–21)	5.86 (4.17)	4.90 (4.15)	0.23	5.66 (4.58)	0.85	6.41 (4.93)	0.524
HADS depression (0–21)	6.86 (3.41)	6.97 (4.09)	0.83	7.41 (4.15)	0.30	7.65 (3.55)	0.176
Fatigue (0–63)	49.08 (11.88)	45.30 (13.71)	0.13	48.21 (11.29)	>0.99	49.00 (13.76)	0.514

HADS, hospital anxiety and depression scale.

TABLE 3. Common Toxicity Criteria for Adverse Event Grades at Each Trial Timepoint

		Baseline		Week 1		Week 5		Week 12	
		n	%	n	%	n	%	n	%
Anorexia	Grade 0/1	31	83.8	31	83.8	30	90.9	17	85.0
	Grade 2	4	10.8	4	10.8	3	9.1	3	15.0
	Grade 3	2	5.4	2	5.4	0	0.0	0	0.0
	Not assessed/deceased	0	0.0	0	0.0	4	0.0	17	0.0
	Total	37	100.0	37	100.0	37	100.0	37	100.0
Dyspnea	Grade 0/1	17	45.9	18	48.6	14	42.4	10	50.0
	Grade 2	17	45.9	17	45.9	15	45.5	6	30.0
	Grade 3	3	8.1	2	5.4	4	12.1	4	20.0
	Not assessed/deceased	0	0.0	0	0.0	4	0.0	17	0.0
	Total	37	100.0	37	100.0	37	100.0	37	100.0
Fatigue	Grade 0/1	13	35.1	15	40.5	12	36.4	9	45.0
	Grade 2	14	37.8	14	37.8	10	30.3	6	30.0
	Grade 3	10	27.0	8	21.6	11	33.3	5	25.0
	Not assessed/ deceased	0	0.0	0	0.0	4	0.0	17	0.0
	Total	37	100.0	37	100.0	37	100.0	37	100.0
Hyperhidrosis	Grade 0/1	35	94.6	37	100.0	31	93.9	20	100.0
	Grade 2	2	5.4	0	0.0	2	6.1	0	0.0
	Not assessed/deceased	0	0.0	0	0.0	4	0.0	17	0.0
	Total	37	100.0	37	100.0	37	100.0	37	100.0
Pain	Grade 0/1	22	59.5	35	94.6	32	97.0	18	90.0
	Grade 2	4	10.8	2	5.4	1	3.0	1	5.0
	Grade 3	11	29.7	0	0.0	0	0.0	1	5.0
	Not assessed/deceased	0	0.0	0	0.0	4	0.0	17	0.0
	Total	37	100.0	37	100.0	37	100.0	37	100.0
Pleuritic pain	Grade 0/1	27	73.0	22	59.5	16	48.5	9	45.0
	Grade 2	7	18.9	6	16.2	10	30.3	6	30.0
	Grade 3	3	8.1	9	24.3	7	21.2	5	25.0
	Not assessed/deceased	0	0.0	0	0.0	4	0.0	17	0.0
	Total	37	100.0	37	100.0	37	100.0	37	100.0

per fraction varies between tumor types and is determined by the α/β ratio of the tumor. Although rapidly proliferating squamous cell carcinomas, such as head and neck or cervical cancer, have high α/β ratios and benefit from treatment with small doses per fraction, many nonsquamous tumors with lower proliferation rates have low α/β ratios and hence benefit from higher doses per fraction.[11,12] Although there are little data from which to estimate the α/β ratio for MPM, its nonsquamous histology, relatively low proliferation index, mesenchymal origin, and apparent radioresistance are all consistent with a low α/β value. This hypofractionated approach would also have the advantage of reducing hospital visits and delivering palliative treatment in a timely fashion, which are clearly important in patients with limited survival, as is the limited toxicity seen here. Therefore, dose escalation studies, ideally delivered using advanced radiotherapy techniques, such as intensity modulated radiotherapy, to help provide adequate coverage of bulky areas of disease, while sparing critical normal tissues including lung and would seem the obvious next step.

TABLE 4. Computed Tomography Response at 12 Weeks Evaluated as per Modified Recist 1.1

		n	%
Assessment of overall response in target lesions	CR	0	0.0
	PR	1	2.5
	SD	13	32.5
	PD	5	12.5
	Not evaluable	21	52.5
	Total	40	100.0

CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease.

There are certain characteristics of the study population that should be highlighted. Only 35% patients had received prior chemotherapy, which is lower than that would be anticipated for patients with MPM. However, the median age of patients in the study was 71 years compared with 60 years in previous studies examining the use of chemotherapy in MPM.[4,5] Furthermore, an epidemiological study showed that, over a 4-year period, only 54 of 146 patients were considered

fit for chemotherapy and of that, only 28 (18%) received chemotherapy.[13] Therefore, the figure reported in the present study appears to be representative of the population from which the study patients were recruited.

The percentage of patients in the study with epithelioid histology was 56.8%. This is perhaps lower than that would have been anticipated and is certainly lower than either of the two phase III chemotherapy trials that showed a survival advantage for cisplatin in combination with an antifolate agent.[4,5] Sarcomatoid histology, seen in 27% of patients in this study compared with between 1% and 8% in those chemotherapy studies, is associated with a significantly worse prognosis than epithelioid histology.[5] This would suggest that patients receiving radiotherapy for pain control are a very different population from those studied in previous chemotherapy trials.

Despite the improvement in pain, there was no improvement in QoL or other symptoms, although there was a trend toward improved QoL in those who responded to radiotherapy. There may be many explanations for this. Primarily, these patients are near the end of life as shown by the median survival of 3.1 months in this trial. QoL naturally deteriorates during this time. In addition, multiple symptoms coexist in MPM, such as dyspnea and fatigue, and these are unlikely to be influenced by an improvement in pain. Similar results have been found in chemotherapy studies in MPM where no QoL improvements have been observed.[3] This may also reflect a generic problem associated with attempts to study QoL outcomes in patients with advanced cancers in which patient attrition and general deterioration make it very difficult to detect treatment-related changes in QoL.

The SYSTEMS trial has limitations. The most obvious of these is the small sample size. However, this was designed as a single arm observational trial, and the main aim was to inform future, larger scale studies; this has been achieved. Another limitation was the very high attrition rate within the trial with only 75% of patients being evaluable 5 weeks after radiotherapy. This highlights the poor survival of these patients and the fact that, by the time most patients with MPM develop significant, uncontrolled chest pain, and they are usually at an advanced stage of their illness. Another potential limitation was the choice of radiotherapy regimen. This is no consensus on the standard radiotherapy technique for treating patients with MPM with palliative intent, so a rather conservative dose and regimen was selected because it was widely used in the study centers. We cannot comment on whether pain improvement persisted beyond 12 weeks as this timepoint was the end of the study.

CONCLUSION

Palliative radiotherapy can be an effective method for treating pain in MPM, and in a proportion of patients is associated with dramatic improvements in pain. These findings provide a foundation for current practice and highlight that radiotherapy studies in complex tumors, such as MPM, are feasible. Dose escalation studies that aim to increase response rates are now eagerly awaited.

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